Löwenberg, C.; Balk, M.; Wischke, C.; Behl, M.; Lendlein, A.:
Shape-Memory Hydrogels: Evolution of Structural Principles To Enable Shape Switching of Hydrophilic Polymer Networks.
In: Accounts of Chemical Research

http://dx.doi.org/10.1021/acs.accounts.6b00584

Shape-Memory Hydrogels: Evolution of structural principles to enable shape switching of hydrophilic polymer networks

Candy Löwenberg [a,#], Maria Balk [a,b,#], Christian Wischke [a,b], Marc Behl [a] and Andreas Lendlein [a,b*]

[a] Institute of Biomaterial Science and Berlin-Brandenburg Center for Regenerative Therapies, Helmholtz-Zentrum Geesthacht, Kantstr. 55, 14513 Teltow, Germany
[b] Helmholtz Virtual Institute "Multifunctional Biomaterials for Medicine", Kanststr. 55, 14513 Teltow, Germany

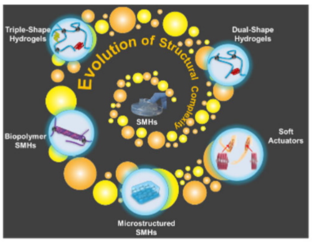
# These authors contributed equally to this work
*e-mail: andreas.lendlein@hzg.de

Conspectus

The ability of hydrophilic chain segments in polymer networks to strongly interact with water allows the volumetric expansion of the material and formation of a hydrogel. When polymer chain segments undergo reversible hydration depending on environmental conditions, smart hydrogels can be realized, which are able to shrink/swell and thus alter their volume on demand. In contrast, implementing the capacity of hydrogels to switch their shape rather than volume demands more sophisticated chemical approaches and structural concepts.

In this article, the principles of hydrogel network design, incorporation of molecular switches, and hydrogel microstructures are summarized that enable a spatially directed actuation of hydrogels by a shape-memory effect (SME) without major volume alteration. The SME involves an elastic deformation (programming) of samples, which are temporarily fixed by reversible covalent or physical crosslinks resulting in a temporary shape. The material can reverse to the original shape when these molecular switches are affected by application of a suitable stimulus. Hydrophobic shape-memory polymers (SMPs), which are established with complex functions including multiple or reversible shape-switching, may provide inspiration for the molecular architecture of shape-memory hydrogels (SMHs), but cannot be identically copied in the world of hydrophilic soft materials. For instance, fixation of the temporary shape requires crosslinks to be formed also in

an aqueous environment, which may not be realized e.g. by crystalline domains from the hydrophilic main chains as these may dissolve in presence of water. Accordingly, dual-shape hydrogels have evolved, where e.g. hydrophobic crystallizable side chains have been linked into hydrophilic polymer networks to act as temperature-sensitive temporary crosslinks. By incorporating a second type of such side chains, triple-shape hydrogels can be realized. Considering the typically given light permeability of hydrogels and the fully hydrated state with easy permeation by small molecules, other types of stimuli like light, pH or ions can be employed that may not be easily used in hydrophobic SMP. In some cases, those molecular switches can respond to more than one stimulus, thus increasing the number of opportunities to induce actuation of these synthetic hydrogels. Beyond this, biopolymer-based hydrogels can be equipped with a shape switching function when facilitating, e.g. triple helix formation in proteins or ionic interactions in polysaccharides. Eventually, microstructured SMHs such as hybrid or porous structures can combine the shape-switching function with an improved performance by helping to overcome frequent shortcomings of hydrogels such as low mechanical strength or volume change upon temporary crosslink cleavage. Specifically, shape switching without major volume alteration is possible in porous SMH by decoupling small volume changes of pore walls on the microscale and the macroscopic sample size. Furthermore, oligomeric rather than short aliphatic side chains as molecular switches allow stabilizing the sample volumes. Based on those structural principles and switching functionalities, SMHs have already entered into applications as soft actuators and are considered, e.g. for cell manipulation in biomedicine. In the context of those applications, switching kinetics, switching forces, and reversibility of switching are aspects to be further explored.



1. Introduction

The capability of a material system to substantially modify its properties upon exposure to altered environmental conditions, i.e. stimuli-sensitivity, is fascinating in terms of both the fundamental principles as well as the applications being enabled. For hydrogels as hydrophilic polymer networks expanded throughout their volume by water, the implementation of stimuli-sensitivity can lead to soft materials that exhibit distinct functions in an aqueous environment e.g. to be used for sensors, processors, actuators, or for compound release.[1]

So far, smart hydrogels that undergo sol-gel transition and swelling-shrinking behavior have found broad attention. In physically crosslinked hydrogels, netpoint formation or cleavage is typically the basis for sol-gel transitions.[2] For covalently crosslinked hydrogels, swelling-shrinking transitions have been induced by changes in temperature, pH or ion concentration depending on the molecular structure of the hydrogel (functional groups, polarity, hydrophilicity, charge).[3] For example, temperature dependence of the hydrogen bonding between water and a polymer with a lower critical solution temperature (LCST) can result in coil to globule transitions, which translate in macroscopic shrinkage upon heating. The inverse behavior, isotropic volume expansion upon heating, can apply for hydrogels with an upper critical solution temperature (UCST).[4]

In contrast to those systems, this Account will focus on the evolution of sophisticated chemical approaches and structural principles that enable a spatially directed movement of shape-memory hydrogels (SMHs) without major alteration of sample volume, which conceptually and mechanistically differ from the above mentioned approaches. As realized predominantly for hydrophobic polymers, the shape-memory effect (SME) allows materials to re-adapt a distinct previous shape in response to an external stimulus,[5] which is possible for macroscopic as well as for microscopic matrices.[6]

Transferring these concepts to SMHs is associated with a number of challenges: In hydrogels, the hydrophilic chain segments connecting the covalent netpoints are in a less coiled, extended state compared to hydrophobic, non-swollen materials, which limits possible deformation for programming SMHs to their temporary shape. The fixation of the temporary shape requires structural elements capable of temporary crosslink formation also in a water-rich environment. Furthermore, temporary crosslink formation and cleavage may lead to changes of the hydrogel properties, such as mechanical strength and, importantly, swellability, which could interfere with the macroscopic effect aimed at. Based on the principles of the SME in hydrophobic polymers, it will be critically analyzed in the following, to which extent the challenges of SMHs have been addressed so far and which future applications may arise.

2. Shape-memory polymers: Switching function enabled by polymer architecture and programming processes

In order to realize a SME in polymers, mandatory requirements are (i) an elastic polymer network structure with netpoints defining the material's permanent shape (chemical netpoints or physical netpoints like crystallites, complexes etc.), (ii) a programming process for elastic deformation of the material, and (iii) molecular switches that provide additional temporary crosslinks to reversibly fix the network in a non-entropic conformation. By application of a stimulus affecting the molecular switches, the polymer chains will regain their full mobility resulting in a directed macroscopic movement. The ability to fix the deformation strain in the temporary shape and to regain the original shape can be quantified by the shape fixity ratio (R_f) and shape recovery ratio (R_r), respectively.[7]

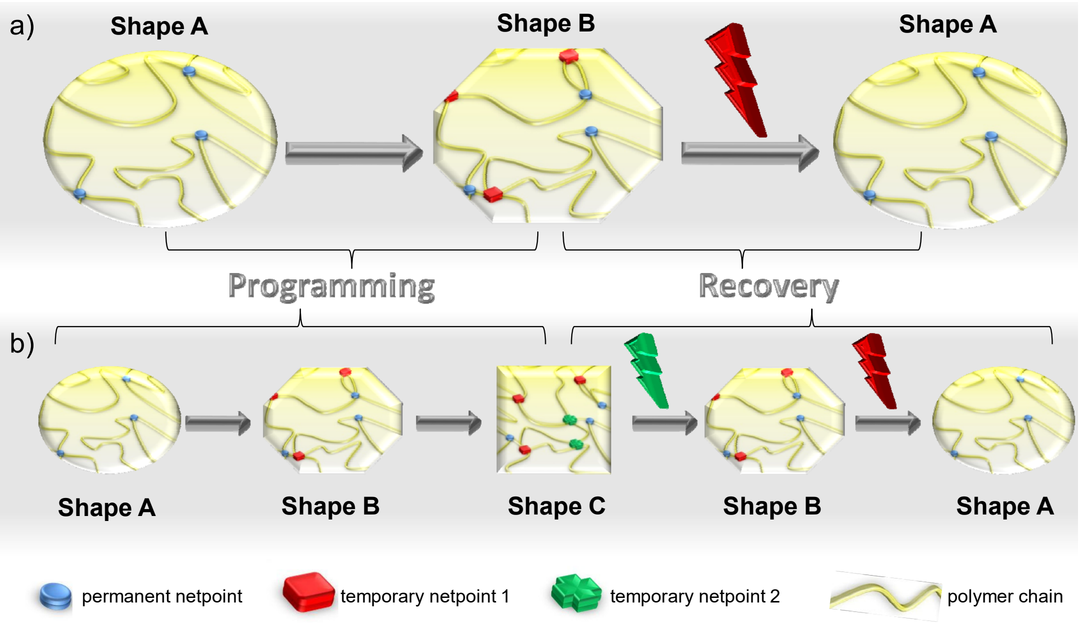


Fig. 1: Illustration of one-way effects for (a) dual- and (b) triple-shape materials.

The shape switching as a one-way effect, named dual-shape effect, from a temporary shape B to a permanent shape A can be designed with numerous individual molecular components for permanent netpoints and temporary crosslinks. For a thermally-induced SME in polymers, domains with a thermal transition temperature T_{trans}, e.g. a glass transition temperature (T_g), a melting temperature (T_m), or a liquid-crystalline phase transition can serve as molecular switches.[8] Here, the programming process typically involves material deformation above the respective T_{trans} to the desired temporary shape (Fig. 1a). This shape is fixed by cooling below T_{trans}, followed by removal of the programming force applied. In thermomechanical experiments, the switching temperature (T_{sw}) can be determined during heating, which correlates to the T_{trans} of the switching domains. T_{sw} can be tailored for a specific application using e.g. copolymers, different chain lengths of the switching segment or the aid of water-induced plasticization.[5]

Triple- or multi-shape polymers can be created when different types of temporary crosslinks (e.g. crystalline domains from different types of chain segments) can be formed and recalled separately (Fig. 1b).[9,10] Examples include copolymer networks with switching domains provided from poly(ε-caprolactone) (PCL) and poly(ethylene glycol) (PEG) or from PCL and poly(cyclohexyl methacrylate).[11] Materials with broad thermal transitions like perfluorosulphonic acid ionomer allow dual-, triple-, or quadruple-shape effects without changes in the material composition.[10]

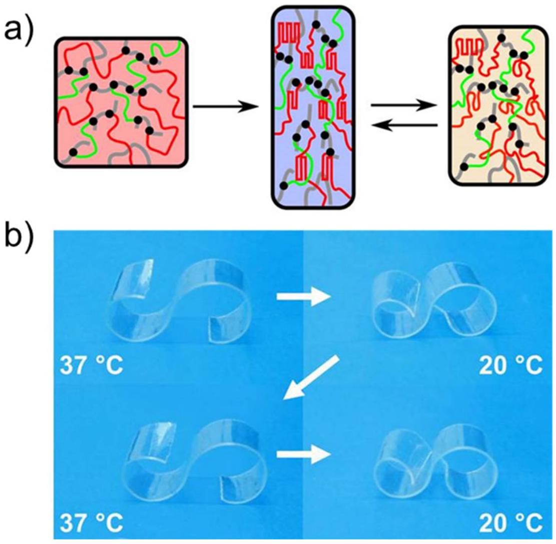


Fig. 2: Fully reversible bidirectional SME of free-standing hydrophobic polymer samples. a) Schematic illustration of the programming to define the shape shifting domains and of the reversible movement by CIE/MIC. b) Macroscopic demonstration of shape shifting. Reproduced with permission from ref. [12]. Copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

In contrast to one-way effects, multiple reversible actuations without intermediate programming require realizing a two-way shape switching. This was first demonstrated under continuous load for crosslinked poly(cyclooctene) networks using crystallization-induced elongation (CIE) and melting-induced contraction (MIC).[13] More recently, the bidirectional SME of freestanding samples was enabled by separating crystallite populations (covering a broad T_m-range) during programming in actuator and shifting-geometry determining domains, thus providing an internal structure to direct CIE/MIC for full reversibility of shape shifting e.g. in PCL based networks (Fig. 2).[12,14]

Heat as the most extensively employed stimulus can also be applied indirectly. For example, incorporation of magnetic nanoparticles (Fe_2O_3 or Fe_3O_4) in SMPs allows inductive heating in an alternating magnetic field.[15] Similarly, Joule heating in an electric field supported by a heat transfer to the switching phase by incorporated carbon nanotubes,[16] photothermal heating based on near-infrared light absorption e.g. of gold nanorods, or application of high-intensity focused ultrasound are further strategies for non-contact thermal stimulation. Molecular switches can also base on reversible chemical reactions such as 2+2 cycloaddition reactions of cinnamic or cinnamylidene acetic acid moieties upon irradiation ($\lambda > 260$ nm), the newly formed bonds can be cleaved again by homolysis at $\lambda < 260$ nm.[17] In case of temperature-sensitive SMPs with hydrophilic chain segments, exposure to water can activate the switching of those materials by water-induced plasticization or solvation of switching domains as shown e.g. for poly(vinyl alcohol) (PVA) networks swelling in water.[18] As automatic switching in presence of water is not always compatible with the goal of creating SMH, alternative network architectures need to be applied as discussed below.

3. Shape-memory effect in hydrogels

3.1 Differentiation between swelling induced movements and SME

Directed movements in hydrogels can be obtained by anisotropic swelling, e.g. by a gradient polymer network structure or by multimaterial approaches with a combination of hydrogel layers of different swellability. Poly(*N*-isopropylacrylamide) (PNIPAm) network films fabricated by photolithography exhibited a LCST with sol-gel/gel-sol transition, at which small-scale modulation in swelling induced a reversible internal mechanical stress and reversible movement.[19] A macroscopic shape transformation from a planar sheet into a helical shape could also be shown for a periodic assembly of stripes of different PNIPAm compositions upon changes of the ionic strength or pH of the medium.[20] Loading of PNIPAm based hydrogels with gold nanoparticles allowed to induce the shape transformation by surface plasmon resonance absorption of the particles and photothermally-induced indirect heating.[21] Furthermore, self-assembly was utilized to direct swelling-induced movements in DNA-based hydrogels. Cytosine-rich amino acid sequences created an i-motif structure by self-assembly at low pH, which dissociated at pH 8 into a random coil formation undergoing a shape transformation into a “quasi-liquid” state.[22]

A key difference between such swelling-induced movements and the SME is the capability of SMHs to fix a temporary shape that can be created from the same sample by elongation, compression, or folding as desired. Control over the direction of movement is given by the reversal of the applied programming deformation once the SMH is actuated.

3.2 SME of synthetic hydrogels: network architectures and concepts for temporary crosslinks

Molecular switches enabling fixation of the temporary shape are typically for SMH not integrated in the main-chain segments of the polymer network, but are pending moieties such as short crystallizable side chains, oligomeric crystallizable side chains, groups for host-guest interactions or complex-forming groups.

The capability of a temperature-induced SME in hydrogels was first demonstrated in poly(acrylic acid)-based networks with short stearyl side chains,[23] in which the hydrophilic main chain segments provided the ability to swell in water, while the dangling stearyl units adopted a crystalline aggregate structure below T_{trans} (physical crosslinks). Upon heating above T_{trans}, the domains from stearyl units became amorphous causing the recovery of the permanent shape and, at the same time, might allow further swelling. Similarly, SMHs could also be realized with further short aliphatic crystallizable side chains e.g. 12-acryloyldodecanoic acid and 16-acryloylhexadecanoic acid.[24,25] In contrast to these hydrogels, SMHs with oligomeric side chains like oligo(*ω*-pentadecalactone) (OPDL) or oligo(tetrahydrofurane) (OTHF) featured an almost temperature independent swelling behavior, which was enabled by the persistent phase segregation of such oligomeric chains into hydrophobic domains even above their T_{trans}. Moreover, in contrast to the short aliphatic switching segments, the oligomeric switching segments were capable of entanglements. The domains formed by the oligomeric side chains were crystalline in the swollen polymer network and showed an isotropic X-ray scattering in the permanent and an anisotropic orientation of crystallites in the elongated temporary shape.[26,27] If crystallizable units as molecular switches should not be coupled to the network structure, they may be physically incorporated leading to double network architectures. In a chemically cross-linked poly(ethylene glycol) hydrogel, interpenetrating poly(vinyl alcohol) (PVA) chains could form crystalline domains created by freezing/thawing cycles to stabilize the temporary shape.[28]

Hydrogels display a condition that allows rapid diffusion of small molecules that may serve as triggers for the SME. When e.g. hydrogen bonding[29], dipole-dipole interactions [30] or ion complexation are used to fix a temporary shape as an alternative to crystallizable domains, these molecular switches could be cleaved by complexing agents, changes of pH or redox reactions. For instance, carboxylic acid containing SMHs enabled the fixation of a temporary shape in the presence of Ca^{2+} solution, with shape recovery after addition of a complexing agent by dissociation of the Ca^{2+}-carboxyl complexes.[31] Dissociation of ionic complexes also occurred by decreasing the pH as shown for hydrogels based on imidazole-zinc complexes.[32] Besides external addition of acid, incorporation of a photoacid generator (PAG) mediating proton release upon UV irradiation[32] or the treatment of the swelling medium with CO_2 resulting in its acidification may allow to induce removal of temporary crosslinks.[33] Furthermore, sensitivity towards redox reactions could be implemented in hydrogels providing selective host-guest interactions between cyclodextrin (CD) and ferrocene in its reduced state acting as temporary crosslinks (Fig. 3).[34] The recovery was initiated by cerium ammonium nitrate (CAN) leading to the oxidation of the central metal ion.

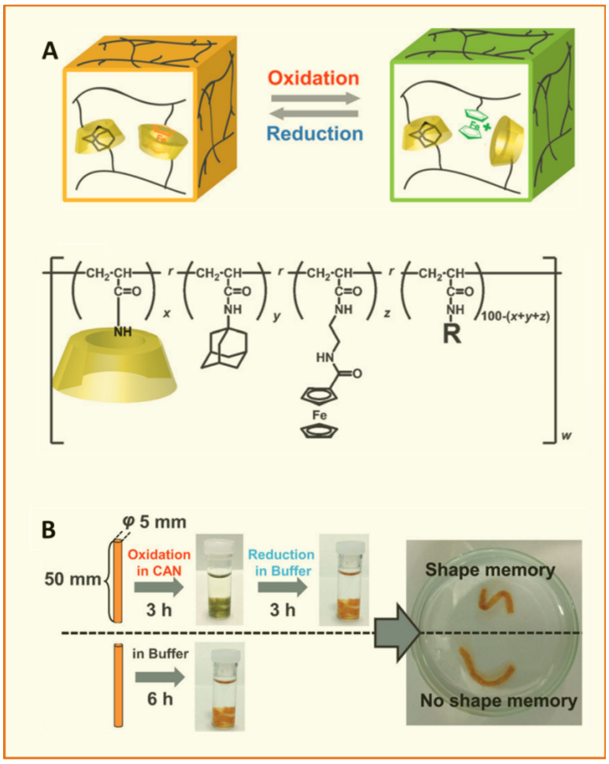


Fig. 3: Redox-sensitive dual-shape hydrogels. A) Mechanism of redox-sensitivity, B) Macroscopic SME demonstration of programming step. Reproduced with permission from ref. [34]. Copyright 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

A response of a SMH to several stimuli may be achieved when either one type of temporary crosslink is sensitive to different stimuli (alternative stimulation) or two types of temporary crosslinks are incorporated in the polymer network structure that respond to independent stimuli (multi-stimuli response). The first approach was realized in a system consisting of PVA and boronic acid, where the formed boronate ester bonds acted as reversible crosslinks.[35] These physical crosslinks could be reversibly formed and cleaved by raising or lowering the pH either directly or via a PAG. In addition, indirect heating by ultrasound treatment could initiate the shape recovery (for further ultrasound-based concepts see section 3.4). The second approach was realized in SMHs with temporary crosslinks based on ionic/complex binding as well as salt-strengthened hydrophobic associations.[36] The hydrogels were prepared by copolymerization of acrylamide and acrylic acid with low amounts of a cationic alkyl side chain, which provided the opportunity of physically crosslinking by salt-dependent hydrophobic association as well as complexation of carboxyl groups and ferric (III) ions. Accordingly, switching could be induced by dissociation of hydrophobic alkyl chains in the presence of water or by the reduction of Fe^{3+} to Fe^{2+} in the presence of ascorbic acid, respectively.

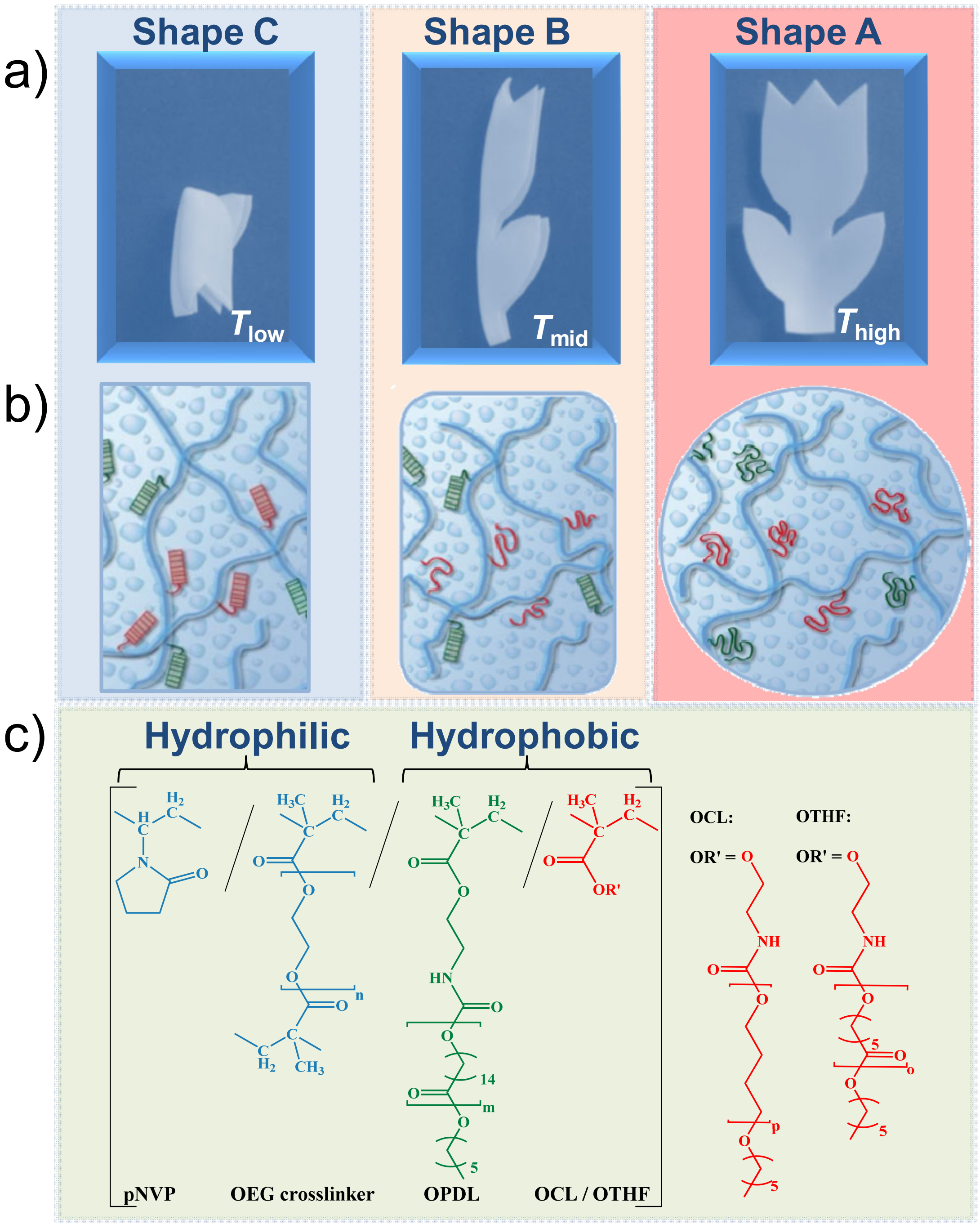


Fig. 4: Triple-shape hydrogels with semi-crystalline side chains. a) Macroscopic demonstration of the recovery process by heat as stimulus. b) Schematic presentation of the network architecture including two types of semi-crystalline side chains (red and green) at different temperatures. c) Chemical structure of the copolymer network.[37] Reproduced with permission from ref. [37]. Copyright 2016 American Chemical Society.

Triple-shape hydrogels (TSHs), which allow two steps of shape switching (compare Fig. 2), can be realized by introducing two different types of crystallizable side chains in a hydrophilic network structure. For example, a copolymer network consisting of oligo(ethylene glycol) (OEG)-crosslinked *N*-vinyl pyrrolidone (NVP) main chains and side chains from OPDL and OCL or from OPDL and OTHF could be recovered to the intermediate and permanent shape by subsequent heating as each combination of side chains had separated thermal transitions of their crystalline domains (Fig. 4).[37] Another approach to design TSHs was realized in a swollen polymer network based on poly[acrylonitrile-*co*-(2-methacryloyloxyethyl phosphorylcholine)].[38] Here, the nitrile groups formed dipole-dipole interactions in deionized water and, at a low concentration of zinc-ions, CN-Zn-CN and CN-CN interactions. Both types of linkages act as temporary crosslinks and dissociate at high zinc concentration, enabling a temperature-independent shape switching in soft materials. A sensitivity of TSHs to further stimuli can be implemented e.g. when photo- and pH-sensitive moieties are incorporated, leading to multi-stimuli responsive hydrogels. In acrylic acid-derived copolymer networks containing host groups (CD) and guest groups (azophenyl derivatives), temporary crosslinks could be formed by the host-guest interactions as well as aggregation of dansyl groups, which are sensitive to light and pH, respectively, allowing complex movements.[39]

3.3 Biopolymers – natural organisation vs. tailorable netpoints

The natural organization of the biopolymer, which is very often sensitive to various kinds of stimuli, can be used for the reversible formation of temporary crosslinks. However, the control of self-organization phenomena is challenging. Therefore, such biopolymer-based SMHs require designing a suitable polymer network architecture, in which the crosslink density plays an important role as it influences swellability, mechanical strength, and SMH elasticity. Nevertheless, the crosslink density should not be too high (steric hindrance of self-organization) and the strength and amount of non-covalent interactions supporting the self-organization have to be considered.

Temporary crosslinks by hydrogen bonding or ionic interaction were the main concepts for the implementation of the SME in biopolymer hydrogels such as from polysaccharides or polypeptides. A thermally-induced SME in peptide-derived hydrogels with collagen-like transient nodes used hydrogen bondings for helix formation and fixation of the temporary shape upon cooling (Fig.5 I).[40] The recovery of the permanent shape was induced by heating and thus melting of triple helices as a result of hydrogen bond cleavage. Furthermore, triple-helices were used for the fixation of temporary shapes in gelatin-based interpenetrating double networks containing graphene oxide.[41] In this system, the shape recovery was induced by the absorption of near-infrared irradiation by the graphene oxide and its subsequent conversion and dissipation of thermal energy.

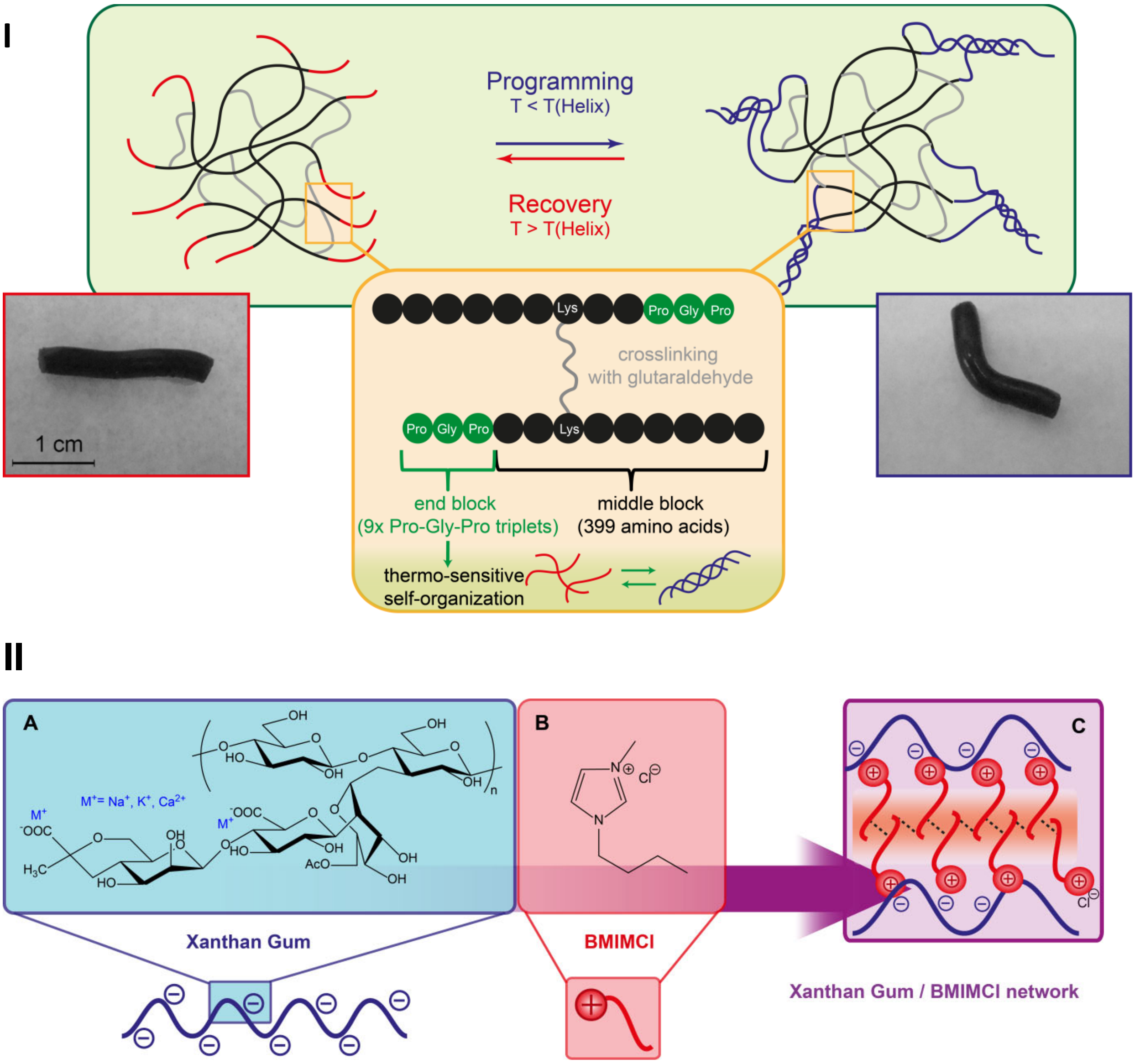


Fig. 5: I) Schematic presentation of the SME in collagen-based hydrogels.[40] Reproduced with permission from ref. [40]. Copyright 2011 American Chemical Society. II) Schematic illustration of network formation between xanthan gum (A) and an ionic liquid (B). The resulting network (C)

consists of imidazolium-carboxylate pairs and intermolecular interactions between the alkyl chains of the ionic liquid.[42] Adapted with permission from ref. [42]

In addition to the concept of natural self-organization, also conventional molecular switches ranging from thermo-sensitive hydrophobic interactions to pH-sensitive boronic esters were exploited for biopolymer-based SMHs. As an example for polysaccharides, xanthan gum incorporating an ionic liquid was able to switch shapes using thermo-sensitive regularly ordered intermolecular interactions acting as temporary crosslinks (Fig. 5 II).[42] The incorporation of reversible PBA-catechol bonds into alginate hydrogels resulted in pH-sensitive SMHs, in which the egg-box-like ionic interactions between alginate and Ca^{2+} acted as permanent netpoints.[43] At alkaline pH, PBA-catechol bonds were formed as temporary crosslinks, while the recovery was induced at acidic pH by the dissociation of PBA-catechol bonds. Furthermore, these hydrogels possessed a multi-stimuli responsiveness as the PBA-diol ester bonds could be reversibly cleaved by sugars.[44]

The combination of the described concepts led to the design of biopolymer-based TSHs. Here, a double network from crosslinked PAAm as well as PBA-grafted alginate-PVA allowed the formation and dissociation of two different types and non-interfering temporary netpoints.[45] In this system, alginate-Ca^{2+} interaction and PBA-diol ester bonds served as independent temporary crosslinks.

3.4 Hydrogel microstructures - Increasing structural complexity for improved functionality

Hydrogels with shape-memory properties could exhibit swelling/deswelling when temporary crosslinks are cleaved/formed. This change of material dimension could interfere with the directed movement and limit the recovery performance and macroscopic effect. The provision of a superstructure, e.g. by the integration of large interconnected pores created by leaching techniques, crosslinking reactions in emulsions, or gas foaming can minimize the transfer of volume change by swelling/deswelling on the microscale to the macroscale and in this way improve material functionality. In addition, a superstructure on the microscale would also facilitate diffusion processes of nutrients, ions, oxygen, and other molecules from the outside to the inside of the material allowing a fast response to an applied stimulus. So far, directed movements in porous hydrogels were realized by stimulation with heat, water, or combination of both.

SMHs with crystallizable switching domains from OCL integrated as side chains in a hydrophilic network architecture from NVP and OEG exhibited a porous micro-structure, which was introduced by a salt-leaching technique. Here, the fixation and recovery were enabled by heat as stimulus and R_f and R_r >80% were observed.[46] Another approach to obtain directed movements was reported for 3D architectured hydrogels consisting of gelatin.[47] These structured hydrogels exhibited a water-induced SME by decreasing the T_g of the system when water is added. In this example, a low water content of polymeric networks is needed to enable the fixation of a temporary shape as temporary crosslinks would be dissolved by equilibrium swelling in water. These porous hydrogels showed a remarkable switching function (R_f up to 85 ± 5% and R_r up to 95 ± 5%). While wet hydrogels recovered their shape after removal of external stress, the dry polymer networks showed plastic deformation in compression tests and recovery of the initial shape upon exposure to water (Figure 6). Porous hydrogels responding to different stimuli were synthesized by dissolving PVA in a high speed mixer followed by freezing in liquid nitrogen.[48] After lyophilization and conditioning at 25 °C and 50% relative humidity, a dual-pore structure, a swelling state below maximum swelling, and two thermal transitions (T_g and T_m) were observed. A temporary shape could be fixed by compression at $T > T_g$ and cooling to $T < T_g$, while shape recovery (R_f = 80%) was initiated by heating at 50% relative humidity. The shape recovery performance could be further improved combining the thermo-sensitivity for temporary shape fixation with a water-induced shape recovery (R_f = 100%).

The structural complexity of porous hydrogels was further increased by implementing a well-defined gradient pore structure as demonstrated for hydrogels obtained from *N*-isopropylacrylamide (NIPAm), 4-hydroxybutyl acrylate, and a heterobifunctional crosslinker.[49] When the main chain forming components were precipitated and crosslinked, a gradient porous morphology was achieved due to the gravitation induced distribution of the resulting chemical netpoints. This gradient pore structure allowed a directed movement by anisotropic swelling in the hydrogels. Furthermore, these 3D-structured hydrogels were able to retain a temporary shape when they were heated and deformed above the LCST of PNIPAm, while the original shape was recovered by water addition.

The implementation of porous structures furthermore allowed extending the stimuli towards using ultrasound as a result of the increased complexity of the materials systems.[50] Instead using ultrasound as a tool for indirect heating, it was successfully applied for the mechanical disruption of temporary crosslinks. Here, the networks consisted of rhodium(I)-phosphine coordination bonds (Rh-PCBs) as well as covalent netpoints. Rh-PCBs were employed as mechanically sensitive molecular switches capable to fix the temporary shape and control the shape recovery upon ultrasound treatment. The porous structure was essential allowing the penetration of ultrasound waves through the interconnected pores, which can induce the collapse of cavitation bubbles inside the macropores and hence improve the efficiency of energy input from ultrasound to the polymer. This example demonstrates how an increase of structural complexity could extend the current mechanisms for the SME as ultrasound could be used before in dry polymer networks only as a source for indirect thermal actuation.

In contrast to porous systems, other approaches concentrated on the design of hybrid compounds to further improve the material properties. Non-porous polymer hydrogels created from bi- or multifunctional chemical crosslinker sometimes display weak mechanical properties with low elongations at break and high brittleness. Therefore, further increase of structural complexity could improve the mechanical strength of soft materials, when hydrogel hybrids were designed. For instance, the strong interactions between carboxyl groups of poly[(acrylic acid)-*co*-(*N*,*N*-dimethylacrylamide)] and TiO_2 particles acting as coordinative cross-linking agents in nanocomposite hydrogels could increase the tensile strength 1.55 times (253 kPa) and the compressive strength 3.1 times (12.7 MPa).[51] In these hydrogels, a water-activated directed movement was achieved when the temporary shape was fixed by drying and the original shape was recovered by immersion in water. Besides hybrid systems combining hydrogels with anorganic materials, polymer-polymer hybrid composites based on poly[(*rac*-lactide)-*co*-glycolide] (PLGA), coated with crosslinked PEGDA hydrogels were designed. After a programming in dry state at 70 °C and cooling, these materials exhibited a water-induced SME by dissolution of PEG crystals and were proposed as potential embolization plug.[52]

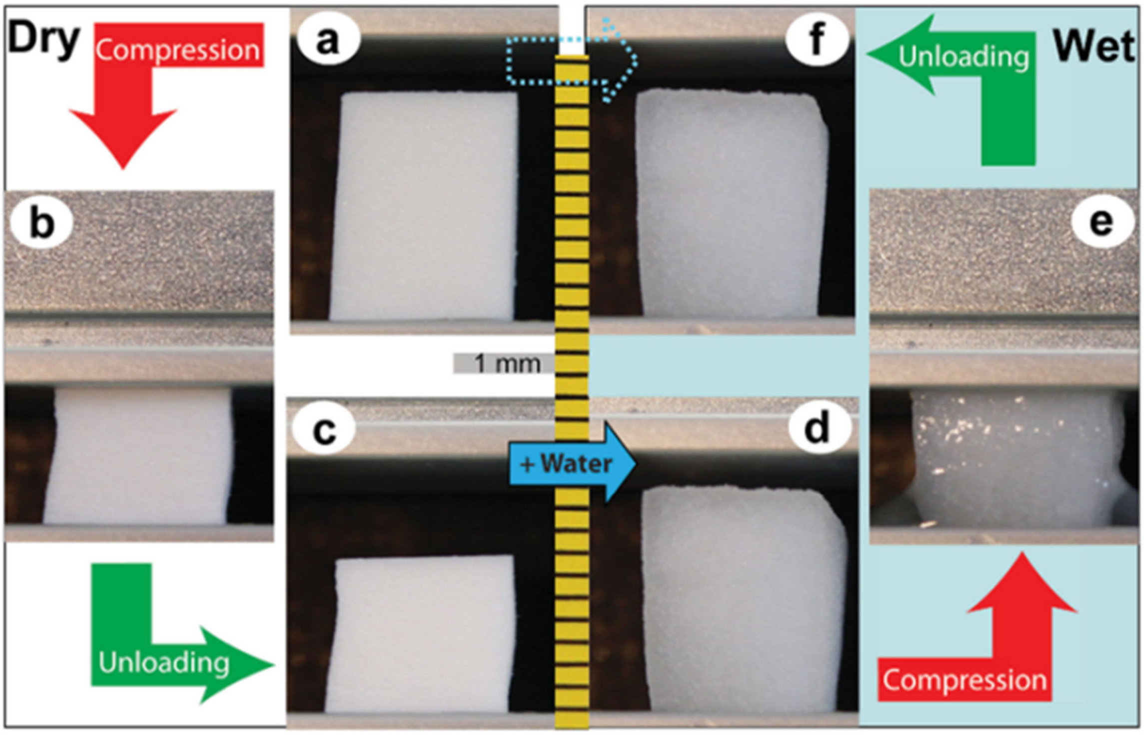


Fig. 6: SME of gelatin-based architectured hydrogels. The temporary shape is fixed by drying of the swollen system (a-b) and the recovery process is induced by water (c-d). A fixation of a

temporary shape in the swollen state could be excluded (d-f).[47] Reproduced with permission from ref. [47]. Copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

4. Future applications from medicine to soft robotics

The development of SMHs can be a technology-push that adds new functionalities to hydrogel materials in existing applications. For instance, the capacity of hydrogels to incorporate bioactive molecules for controlled delivery,[53] being of interest particularly for sensitive factors that demand aqueous environment, can be expanded to a stimuli-sensitive anchoring of drug loaded devices in body cavities e.g. after oral administration or after minimally invasive implantation in the abdomen, urogenital, or vaginal tract. Spatially directed movements of SMHs at the macro- or microscale may be used to seal containers after filling with sensitive compounds, i.e. using the shape recovery *ex vivo* before implantation.[54] Furthermore, on a molecular level, switchable network structures or morphologies of SMHs may allow rapid drug loading into the bulk phase during the programming step, where temporary crosslinks are transitory removed. Accordingly, enhanced release rates may also be induced along with crosslink cleavage for shape recovery as well as subsequently in a step-wise fashion by repeated application of the stimulus until reservoir exhaustion. In some cases, ions used as temporary crosslinks may have additional beneficial biological effects when continuously released from SMHs.[55]

Innovation by SMHs can be expected also in the context cell manipulation, as cells are not only responding to material softness but also to (repetitive) mechanical load or spatial position in a 3D environment. A beneficial effect of functionalizing a PCL/PEG-based SMH with Arg-Gly-Asp (RGD) peptide sequences was reported for enhanced cell adhesion and spreading.[56] SMH sheets can protect pre-cultured cells during insertion by adapting a curled shape.[57] An ion-sensitive SMH synthesized from acrylonitrile, AA, and *N*,*N'*-bis(acryloyl)cystamine crosslinker, which could switch from a planar shape to a cube, illustrated effects of localization) on the spreading and differentiation of human mesenchymal stem cells (hMSCs) to adipogenic or osteogenic cell lineages, possibly due to effects of microgravity on cytoskeleton organisation (Figure 7).[58] In the context of soft tissue engineering, porosity of hydrogels is essential to secure diffusion of oxygen, nutrients, and cells enabling e.g. local angiogenesis.[59] Once combined with a shape switching that locally alters the cell environment (e.g. altered pore shape), local stretching of cells[47] or migration to other biological compartments may be initialized.

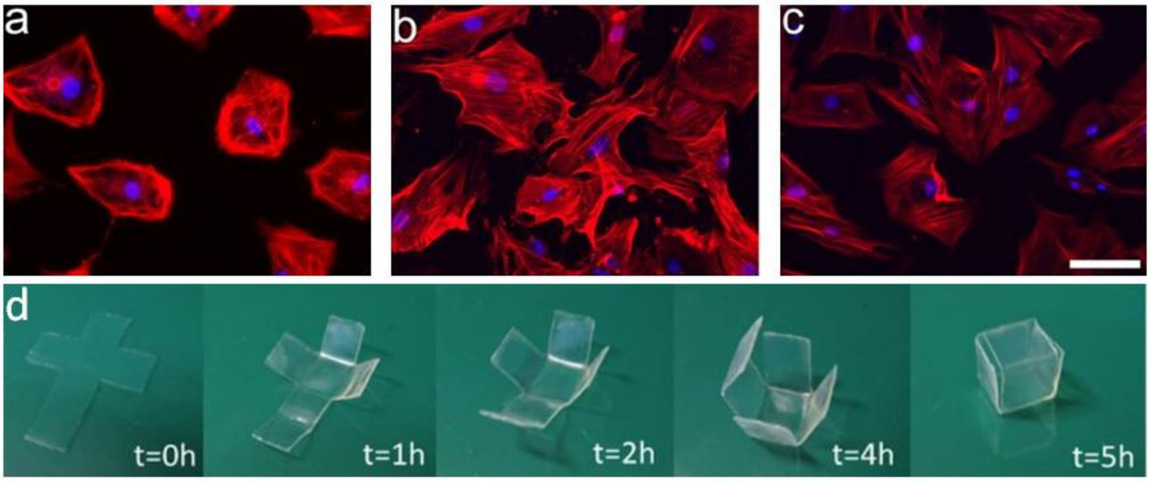


Fig. 7: Fluorescent micrographs of stained hMSCs, which were cultured on the a) top, b) side, and c) bottom surface of d) a SMH cube.[58] Scale bar (a-c), 30 µm. Reproduced with permission from ref. [58]. Copyright 2014 Macmillan Publishers Ltd: Scientific Reports.

Thinking about further technological fields for smart actuators, applications as artificial muscles, soft robotics for delicate applications, or micro swimmers may be future goals (Figure 8). In particular, hydrogels could be used in soft robotics, which describes engineered mobile machines, created by soft materials. In contrast to conventional robots basing on tough components (e.g., steel) and enabling directed movements by electric motors, soft robots are suitable for applications in natural environments, while preventing mechanical damage of their environment. In case of soft robots from SMHs, the activation process can be realized by the SME providing applications as pneumatic actuators, grippers, and microswimmers. Especially soft robots composed from hydrogels represent an upcoming class as their actuation is not limited to the stimuli potentially applicable to nonswollen systems. Here, actuations can be realized that require diffusion processes, that is, ion- or signaling molecule-mediated shape switches, as demonstrated for SMHs being sensitive to ions, salts, glucose, changes in pH value, or redox potential. [60] In order to allow SMHs to enter into these fields, switching kinetics, created switching forces, and reversibility of switching are aspects to be considered and further explored. Switching mechanisms realized for hydrophobic SMPs or design concepts based on multiple materials as in case of an SMP-coated artificial muscle[61] may provide inspiration on this path.

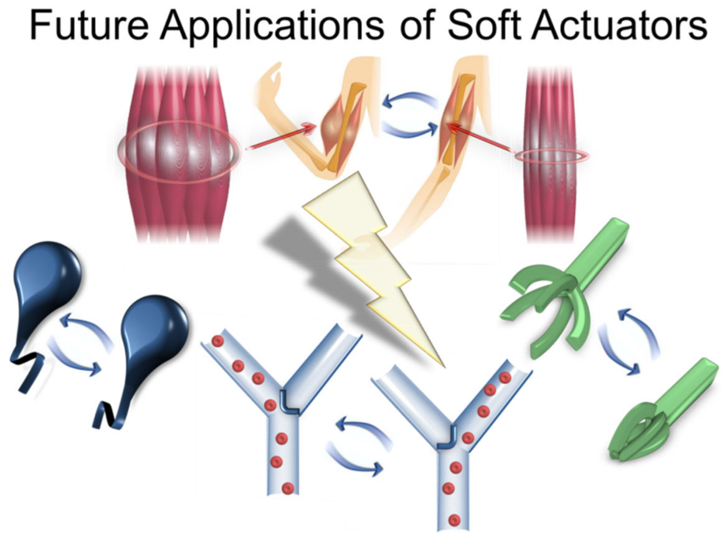


Fig. 8: Vision of future application of SMHs.

5. Conclusions

This article illustrated that some structural principles predominately employed in hydrophobic SMPs to realize a shape-switch by the SME could also be transferred to hydrogels. Importantly, key challenges such as preservation of sample volume upon switching could be addressed by employing phase segregated oligomeric side chains as molecular switches or using hydrogels with a porous internal structure. Beyond classical stimuli for SMP like heat, hydrogels enable the use of further stimuli including pH, light, ions and other components that can diffuse in a water-rich polymer network to interact with temporary crosslinks and induce dual- or triple-shape effects. Even higher levels of complexity are given for biopolymers and, eventually, hybrid/porous systems, where a tailoring of formed structures is key to material function. It can be anticipated that the recent advances such as the variety of stimuli to initiate the switching process will be transferred to more complex systems in order to improve the functionality and to meet the intricate demands of future applications from medicine to smart technical actuators including soft robotics.

Biographical Information

Candy Löwenberg obtained her Ph.D. in Materials in Life Sciences from the University of Potsdam and is currently working as PostDoc at the Institute of Biomaterial Science (IBS) of the Helmholtz-Zentrum Geesthacht in Teltow, Germany.

Maria Balk received her Ph.D. in Materials in Life Sciences at the University of Potsdam and is currently working as PostDoc at IBS.

Christian Wischke holds a Ph.D. in Pharmaceutical Sciences from Freie Universität Berlin and is currently heading the department Pharmaceutical Technology at IBS.

Marc Behl received his Ph.D. degree in Organic Chemistry from the Johannes Gutenberg University Mainz. Currently, he is head of the Active Polymers Department at IBS.

Andreas Lendlein is the Director of the Institute of Biomaterial Science. He completed his Habilitation in Macromolecular Chemistry in 2002 at RWTH Aachen University and received his doctoral degree in Materials Science from the Swiss Federal Institute of Technology (ETHZ) in Zürich.

Acknowledgements

The authors thank the Helmholtz Association for funding of this work through programme-oriented funding, Helmholtz Cross Programme Initiative "Technology and Medicine - Adaptive Systems" and through Helmholtz Virtual Institute “Multifunctional Materials for Medicine" (VH-VI-423).

References

(1) Yoshida, R.; Okano, T.: Stimuli-Responsive Hydrogels and Their Application to Functional Materials. In *Biomedical Applications of Hydrogels Handbook*; Ottenbrite, R. M., Park, K., Okano, T., Eds.; Springer New York: New York, NY, 2010; pp 19-43.

(2) Jeong, B.; Kim, S. W.; Bae, Y. H. Thermosensitive sol-gel reversible hydrogels. *Adv. Drug Del. Rev.* **2002**, *54*, 37-51.

(3) Nebhani, L.; Choudhary, V.; Adler, H.-J.; Kuckling, D. pH- and Metal Ion- Sensitive Hydrogels based on N-[2-(dimethylaminoethyl)acrylamide]. *Polymers* **2016**, *8*, 233.

(4) Gandhi, A.; Paul, A.; Sen, S. O.; Sen, K. K. Studies on thermoresponsive polymers: Phase behaviour, drug delivery and biomedical applications. *Asian J. Pharm. Sci.* **2015**, *10*, 99-107.

(5) Lendlein, A.; Behl, M.; Hiebl, B.; Wischke, C. Shape-memory polymers as a technology platform for biomedical applications. *Expert Rev. Med. Devices* **2010**, *7*, 357-379.

(6) Wischke, C.; Lendlein, A. Method for Preparation, Programming, and Characterization of Miniaturized Particulate Shape-Memory Polymer Matrices. *Langmuir* **2014**, *30*, 2820-2827.

(7) Wagermaier, W.; Kratz, K.; Heuchel, M.; Lendlein, A. Characterization Methods for Shape-Memory Polymers. *Adv. Polym. Sci.* **2010**, *226*, 97-145.

(8) Julich-Gruner, K. K.; Löwenberg, C.; Neffe, A. T.; Behl, M.; Lendlein, A. Recent Trends in the Chemistry of Shape-Memory Polymers. *Macromol. Chem. Phys.* **2013**, *214*, 527-536.

(9) Zotzmann, J.; Behl, M.; Feng, Y.; Lendlein, A. Copolymer Networks Based on Poly(omega-pentadecalactone) and Poly(epsilon-caprolactone) Segments as a Versatile Triple-Shape Polymer System. *Adv. Funct. Mater.* **2010**, *20*, 3583-3594.

(10) Xie, T. Tunable polymer multi-shape memory effect. *Nature* **2010**, *464*, 267-270.

(11) Bellin, I.; Kelch, S.; Langer, R.; Lendlein, A. Polymeric triple-shape materials. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 18043-18047.

(12) Saatchi, M.; Behl, M.; Nöchel, U.; Lendlein, A. Copolymer Networks From Oligo(epsilon-caprolactone) and n-Butyl Acrylate Enable a Reversible Bidirectional Shape-Memory Effect at Human Body Temperature. *Macromol. Rapid Commun.* **2015**, *36*, 880-884.

(13) Chung, T.; Romo-Uribe, A.; Mather, P. T. Two-Way Reversible Shape Memory in a Semicrystalline Network. *Macromolecules* **2008**, *41*, 184-192.

(14) Behl, M.; Kratz, K.; Noechel, U.; Sauter, T.; Lendlein, A. Temperature-memory polymer actuators. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 12555-12559.

(15) Razzaq, M. Y.; Behl, M.; Lendlein, A. Memory-effects of magnetic nanocomposites. *Nanoscale* **2012**, *4*, 6181-6195.

(16) Jung, Y. C.; Yoo, H. J.; Kim, Y. A.; Cho, J. W.; Endo, M. Electroactive shape memory performance of polyurethane composite having homogeneously dispersed and covalently crosslinked carbon nanotubes. *Carbon* **2010**, *48*, 1598-1603.

(17) Lendlein, A.; Jiang, H.; Jünger, O.; Langer, R. Light-induced shape-memory polymers. *Nature* **2005**, *434*, 879-882.

(18) Du, H.; Zhang, J. Solvent induced shape recovery of shape memory polymer based on chemically cross-linked poly(vinyl alcohol). *Soft Matter* **2010**, *6*, 3370-3376.

(19) Zhang, Y.; Ionov, L. Reversibly Cross-Linkable Thermoresponsive Self-Folding Hydrogel Films. *Langmuir* **2015**, *31*, 4552-4557.

(20) Wu, Z. L.: M. Moshe, J. Greener, H. Thérien-Aubin, Z. H. Nie, E. Sharon, E. Kumacheva, *Nat. Commun.* **2013**, *4*, 1586.

(21) Zhao, J.; Fang, C.; Zhu, Y.; He, G.; Pan, F.; Jiang, Z.; Zhang, P.; Cao, X.; Wang, B. Manipulating the interfacial interactions of composite membranes via a mussel-inspired approach for enhanced separation selectivity. *J. Mater. Chem. A* **2015**, *3*, 19980-19988.

(22) Guo, W.; Lu, C.-H.; Orbach, R.; Wang, F.; Qi, X.-J.; Cecconello, A.; Seliktar, D.; Willner, I. pH-Stimulated DNA Hydrogels Exhibiting Shape-Memory Properties. *Adv. Mater.* **2015**, *27*, 73-78.

(23) Osada, Y.; Matsuda, A. Shape memory in hydrogels. *Nature* **1995**, *376*, 219.

(24) Uchida, M.; Kurosawa, M.; Osada, Y. Swelling Process and Order-Disorder Transition of Hydrogel Containing Hydrophobic Ionizable Groups. *Macromolecules* **1995**, *28*, 4583-4586.

(25) Mitsumata, T.; Gong, J. P.; Osada, Y. Shape memory functions and motility of amphiphilic polymer gels. *Polym. Adv. Technol.* **2001**, *12*, 136-150.

(26) Balk, M.; Behl, M.; Nöchel, U.; Lendlein, A. Shape-Memory Hydrogels with Switching Segments Based on Oligo(ω-pentadecalactone). *Macromol. Mater. Eng.* **2012**, *297*, 1184-1192.

(27) Balk, M.; Behl, M.; Nöchel, U.; Lendlein, A. Shape-Memory Hydrogels with Crystallizable Oligotetrahydrofuran Side Chains. *Macromol. Symp.* **2014**, *345*, 8-13.

(28) Li, G.; Zhang, H. J.; Fortin, D.; Xia, H. S.; Zhao, Y. Poly(vinyl alcohol)-Poly(ethylene glycol) Double-Network Hydrogel: A General Approach to Shape Memory and Self-Healing Functionalities. *Langmuir* **2015**, *31*, 11709-11716.

(29) Yasin, A.; Zhou, W. F.; Yang, H. Y.; Li, H. Z.; Chen, Y.; Zhang, X. Y. Shape Memory Hydrogel based on a Hydrophobically-Modified Polyacrylamide (HMPAM)/alpha-CD Mixture via a Host-Guest Approach. *Macromol. Rapid Commun.* **2015**, *36*, 845-851.

(30) Zhang, Y. Y.; Li, Y. M.; Liu, W. G. Dipole-Dipole and H-Bonding Interactions Significantly Enhance the Multifaceted Mechanical Properties of Thermoresponsive Shape Memory Hydrogels. *Adv. Funct. Mater.* **2015**, *25*, 471-480.

(31) Ren, Z. Q.; Zhang, Y. Y.; Li, Y. M.; Xu, B.; Liu, W. G. Hydrogen bonded and ionically crosslinked high strength hydrogels exhibiting Ca2+-triggered shape memory properties and volume shrinkage for cell detachment. *J. Mater. Chem. B* **2015**, *3*, 6347-6354.

(32) Feng, W.; Zhou, W. F.; Zhang, S. D.; Fan, Y. J.; Yasin, A.; Yang, H. Y. UV-controlled shape memory

hydrogels triggered by photoacid generator. *RSC Adv.* **2015**, *5*, 81784-81789.

(33) Xu, B.; Zhang, Y. Y.; Liu, W. G. Hydrogen-Bonding Toughened Hydrogels and Emerging CO2-Responsive Shape Memory Effect. *Macromol. Rapid Commun.* **2015**, *36*, 1585-1591.

(34) Miyamae, K.; Nakahata, M.; Takashima, Y.; Harada, A. Self-Healing, Expansion-Contraction, and Shape-Memory Properties of a Preorganized Supramolecular Hydrogel through Host-Guest Interactions. *Angew. Chem. Int. Edit.* **2015**, *54*, 8984-8987.

(35) Li, G.; Yan, Q.; Xia, H.; Zhao, Y. Therapeutic-Ultrasound-Triggered Shape Memory of a Melamine-Enhanced Poly(vinyl alcohol) Physical Hydrogel. *ACS Appl. Mater. Interfaces* **2015**, *7*, 12067-12073.

(36) Fan, Y. J.; Zhou, W. F.; Yasin, A.; Li, H. Z.; Yang, H. Y. Dual-responsive shape memory hydrogels with novel thermoplasticity based on a hydrophobically modified polyampholyte. *Soft Matter* **2015**, *11*, 4218-4225.

(37) Nöchel, U.; Behl, M.; Balk, M.; Lendlein, A. Thermally-Induced Triple-Shape Hydrogels: Soft Materials Enabling Complex Movements. *ACS Appl. Mater. Interfaces* **2016**, *8*, 28068–28076.

(38) Han, Y.; Bai, T.; Liu, Y.; Zhai, X.; Liu, W. Zinc ion uniquely induced triple shape memory effect of dipole-dipole reinforced ultra-high strength hydrogels. *Macromol. Rapid Commun.* **2012**, *33*, 225-231.

(39) Xiao, Y.-Y.; Gong, X.-L.; Kang, Y.; Jiang, Z.-C.; Zhang, S.; Li, B.-J. Light-, pH- and thermal-responsive hydrogels with the triple-shape memory effect. *Chem. Commun.* **2016**, *52*, 10609-10612.

(40) Skrzeszewska, P. J.; Jong, L. N.; de Wolf, F. A.; Cohen Stuart, M. A.; van der Gucht, J. Shape-Memory Effects in Biopolymer Networks with Collagen-Like Transient Nodes. *Biomacromolecules* **2011**, *12*, 2285-2292.

(41) Huang, J. H.; Zhao, L.; Wang, T.; Sun, W. X.; Tong, Z. NIR-Triggered Rapid Shape Memory PAM-GO-Gelatin Hydrogels with High Mechanical Strength. *ACS Appl. Mater. Interfaces* **2016**, *8*, 12384-12392.

(42) Izawa, H.; Kadokawa, J.-i. Preparation and characterizations of functional ionic liquid-gel and hydrogel materials of xanthan gum. *J. Mater. Chem.* **2010**, *20*, 5235-5241.

(43) Li, Z. W.; Lu, W.; Ngai, T.; Le, X. X.; Zheng, J.; Zhao, N.; Huang, Y. J.; Wen, X. F.; Zhang, J. W.; Chen, T. Mussel-inspired multifunctional supramolecular hydrogels with self-healing, shape memory and adhesive properties. *Polym. Chem.* **2016**, *7*, 5343-5346.

(44) Meng, H.; Zheng, J.; Wen, X. F.; Cai, Z. Q.; Zhang, J. W.; Chen, T. pH- and Sugar-Induced Shape Memory Hydrogel Based on Reversible Phenylboronic Acid-Diol Ester Bonds. *Macromol. Rapid Commun.* **2015**, *36*, 533-537.

(45) Le, X.; Lu, W.; Zheng, J.; Tong, D.; Zhao, N.; Ma, C.; Xiao, H.; Zhang, J.; Huang, Y.; Chen, T. Stretchable supramolecular hydrogels with triple shape memory effect. *Chem. Sci.* **2016**, *7*, 6715-6720.

(46) Balk, M.; Behl, M.; Nöchel, U.; Lendlein, A. Architectured Shape-Memory Hydrogels with Switching Segments Based on Oligo(ε-caprolactone). *MRS Advances* **2016**, *1*, 2011-2017.

(47) Neffe, A. T.; Pierce, B. F.; Tronci, G.; Ma, N.; Pittermann, E.; Gebauer, T.; Frank, O.; Schossig, M.; Xu, X.; Willie, B. M.; Forner, M.; Ellinghaus, A.; Lienau, J.; Duda, G. N.; Lendlein, A. Hydrogels: One Step Creation of Multifunctional 3D Architectured Hydrogels Inducing Bone Regeneration. *Adv. Mater.* **2015**, *27*, 1738-1744.

(48) Bonadies, I.; Izzo Renzi, A.; Cocca, M.; Avella, M.; Carfagna, C.; Persico, P. Heat Storage and Dimensional Stability of Poly(vinyl alcohol) Based Foams Containing Microencapsulated Phase Change Materials. *Ind. Eng. Chem. Res.* **2015**, *54*, 9342-9350.

(49) Luo, R.; Wu, J.; Dinh, N.-D.; Chen, C.-H. Gradient Porous Elastic Hydrogels with Shape-Memory Property and Anisotropic Responses for Programmable Locomotion. *Adv. Funct. Mater.* **2015**, *25*, 7272-7279.

(50) Zhang, P.; Behl, M.; Peng, X.; Razzaq, M. Y.; Lendlein, A. Ultrasonic Cavitation Induced Shape-Memory Effect in Porous Polymer Networks. *Macromol. Rapid Commun.* **2016**, *37*, 1849-1977.

(51) Xu, B.; Li, H.; Wang, Y.; Zhang, G.; Zhang, Q. Nanocomposite hydrogels with high strength cross-linked by titania. *RSC Adv.* **2013**, *3*, 7233-7236.

(52) Wong, Y. S.; Salvekar, A. V.; Zhuang, K. D.; Liu, H.; Birch, W. R.; Tay, K. H.; Huang, W. M.;

Venkatraman, S. S. Bioabsorbable radiopaque water-responsive shape memory embolization plug for temporary vascular occlusion. *Biomaterials* **2016**, *102*, 98-106.

(53) Zhang, X.; Zhou, H.; Xie, Y.; Ren, C.; Ding, D.; Long, J.; Yang, Z. Rational Design of Multifunctional Hetero-Hexameric Proteins for Hydrogel Formation and Controlled Delivery of Bioactive Molecules. *Adv. Healthcare Mater.* **2014**, *3*, 1804-1811.

(54) Kozlovskaya, V.; Kharlampieva, E.; Mansfield, M. L.; Sukhishvili, S. A. Poly(methacrylic acid) Hydrogel Films and Capsules: Response to pH and Ionic Strength, and Encapsulation of Macromolecules. *Chem. Mater.* **2006**, *18*, 328-336.

(55) Xu, B.; Li, Y.; Gao, F.; Zhai, X.; Sun, M.; Lu, W.; Cao, Z.; Liu, W. High Strength Multifunctional Multiwalled Hydrogel Tubes: Ion-Triggered Shape Memory, Antibacterial, and Anti-inflammatory Efficacies. *ACS Appl. Mater. Interfaces* **2015**, *7*, 16865-16872.

(56) Xu, X.; Davis, K. A.; Yang, P.; Gu, X.; Henderson, J. H.; Mather, P. T. Shape Memory RGD-Containing Networks: Synthesis, Characterization, and Application in Cell Culture. *Macromol. Symp.* **2011**, *309-310*, 162-172.

(57) Nan, W.; Wang, W.; Gao, H.; Liu, W. Fabrication of a shape memory hydrogel based on imidazole-zinc ion coordination for potential cell-encapsulating tubular scaffold application. *Soft Matter* **2013**, *9*, 132-137.

(58) Han, Y.; Bai, T.; Liu, W. Controlled Heterogeneous Stem Cell Differentiation on a Shape Memory Hydrogel Surface. *Sci. Rep.* **2014**, *4*, 5815.

(59) Annabi, N.; Nichol, J. W.; Zhong, X.; Ji, C.; Koshy, S.; Khademhosseini, A.; Dehghani, F. Controlling the porosity and microarchitecture of hydrogels for tissue engineering. *Tissue Eng. Part B Rev.* **2010**, *16*, 371-383.

(60) Trimmer, B. Soft robots. *Curr. Biol.* **2013**, *23*, R639-R641.

(61) Takashima, K.; Rossiter, J.; Mukai, T. McKibben artificial muscle using shape-memory polymer. *Sens. Actuators, A* **2010**, *164*, 116-124.